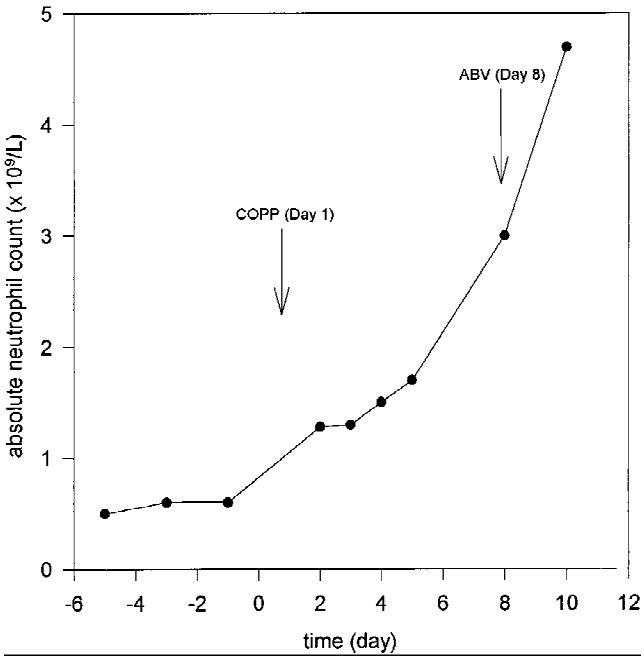

Fig. 2. Rise of leukocyte count without drop nor nadir during first induction with intensive chemotherapy.

nosis, in contrast to RHS associated with peripheral T-cell lymphoma, in which RHS may be a terminal event after a stable course for variable periods [2]. In previous studies of a total of 55 Hodgkin's disease patients with marrow involvement, prominent hemophagocytic histocytosis were not described [5,6].

Although our patient has stage IV Hodgkin's disease, its focal involvement could not explain the profound pancytopenia. Moreover, a previous study [5] of 36 marrow-positive Hodgkin's disease patients showed most to have normal blood counts. Moreover, in another study of Hodgkin's disease with marrow involvement [6], when combination chemotherapy (MOPP) was given to the patients with initial leukopenia, severe leukopenia occurred, with 42.8% developing life-threatening infections. In our patient, despite the severe initial neutropenia, the leukocyte count actually rose, instead of dropping, during the initial phase of induction chemotherapy (Fig. 2), and our patient tolerated the chemotherapy very well without complications. Although marrow-positive Hodgkin's disease with non-RHS leukopenia was reported to have a poor prognosis due to a low remission rate [6], our patient illustrated that RHS-associated leukopenia in Hodgkin's disease could respond favourably to chemotherapy.

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Low Levels of Plasma Stem-Cell Factor in a Patient With Cyclic Neutropenia

To the Editor: Cyclic neutropenia is a rare disorder occurring in children and adults. However, the pathogenetic mechanism is unknown [1]. The proposed mechanisms involve a defect in the production of hematopoietic stem cells, mainly in granulopoiesis, or immunological abnormality as evidenced by the excess of large granular lymphocytes and the response to immunosuppressive agents [1]. Although cycling is most prominent in neutrophils, fluctuations have been observed in all blood components [1]. Thus, there may be fundamental defects in hematopoiesis affecting the production of all lineages of hematopoietic stem cells, or in the function of the microenvironment of the bone-marrow stroma supporting hematopoiesis.

We previously reported fluctuation in plasma cytokine levels in a patient wtih cyclic neutropenia; the greatest fluctuation was found in G-CSF, and the TNF-α level fluctuated inversely with that of G-CSF, while oscillation of IL-6 preceded that at the G-CSF level [2].

The administration of growth factors such as G-CSF increased the peripheral blood neutrophil count but amplified oscillation, and GM-CSF also eliminated the multilineage oscillation of circulating blood elements [3].

It is known that c-kit is expressed on early hematopoietic progenitors, while stem-cell factor (SCF), which is a ligand for c-kit, is expressed only by stromal cells including endothelial cells and fibroblasts, and serves as a multipoietin which acts on early hematopoietic progenitors in synergy with other cytokines such as IL-3, IL-6, and G-CSF [4]. SCF also exists as a soluble form by means of proteolysis in the plasma [4]. We measured the plasma levels of SCF to determine the pathogenesis of cyclic neutropenia.

The patient was a 35-year-old female with cyclic neutropenia with a 21-day cycle, that had been diagnosed at age 10.

Blood was drawn and anticoagulated with EDTA. Plasma was separated immediately by centrifugation, and frozen at −80°C until assay. Levels of SCF were measured by the sandwich enzyme immunoassay technique, using a Quantikine human SCF immunoassay kit (R&D Systems, MN).

SCF levels were below normal range at all points of measurement (normal range (mean ± SD), 1,622 ± 314 pg/ml) (Fig. 1). However, those levels did not fluctuate significantly, with fluctuations in each element of leukocytes.

The significance of the low levels of SCF at all points of measurement during one cycle of neutropenia is not clear. In aplastic anemia and myelodysplastic syndrome, plasma levels of Epo and G-CSF were increased due to increased endogenous production in contrast to low levels of plasma SCF, suggesting abnormalities of cells within the microenvironment [5,6]. There may be a fundamental defect of hematopoiesis in the early stages of hematopoiesis in cyclic neutropenia as a defect of production of growth factor or as a defect in the function of microenvironment, as supposed in aplastic anemia. The feedback mechanism for the production of soluble SCF may be nonfunctional in cyclic neutropenia, as in aplastic anemia and myelodysplastic syndrome of bone-marrow failure [5,6]. The absence of significant fluctuation in the levels of SCF might indicate that small changes in SCF concentration could exert a major effect on hematopoiesis. However, the mechanism of cycling of blood elements still could not be explained in this context.

SCF primarily exists attached to stromal cells, which functions more significantly than the soluble form [4]. Further measurement of the m-RNA gene of SCF in bone-marrow stromal cells, and of their transcription prod-

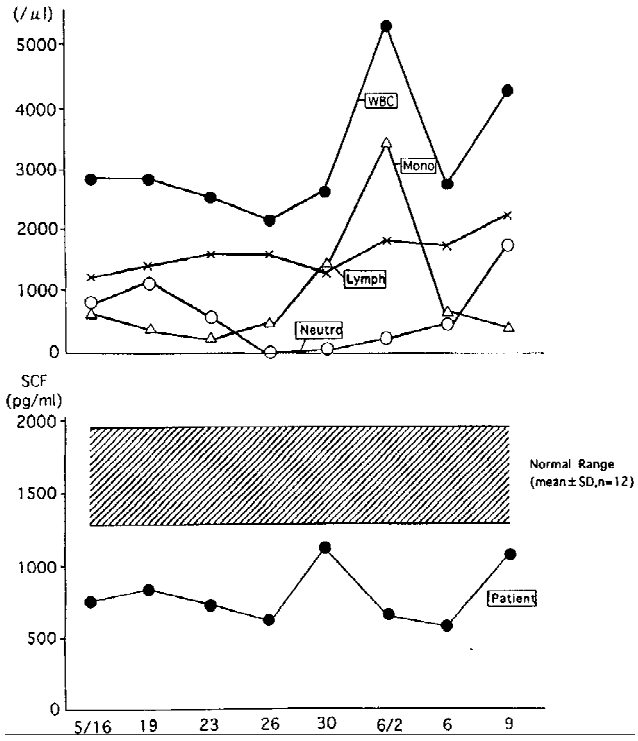

Fig. 1. Top: Fluctuations in hematological values. Bottom: Levels of plasma-soluble stem-cell factor (SCF). Mean value of duplicate determinations is shown.

uct in cyclic neutropenia, may more directly demonstrate the function of bone-marrow stromal cells in this disorder.

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Erythropoietin Permits High-Dose Chemotherapy With Peripheral Blood Stem-Cell Transplant for a Jehovah's Witness

To the Editor: Due to their religious conviction prohibiting the receipt of blood products, Jehovah's Witnesses with leukemia and lymphoma preclude themselves from many of the more aggressive neoplastic treatments, such as high-dose chemotherapy. Although Jehovah's Witnesses safely undergo major operative procedures and standard-dose chemotherapy, there are very few reports of these individuals being offered more intensive marrow-ablative chemotherapy, even in potentially curative situations. One previous case describes the treatment of a Jehovah's Witness with high-dose cytarabine after a second relapse of his acute monocytic leukemia [1]. High-dose chemotherapy, even with bone-marrow or peripheral blood stem-cell support, places patients at risk for infections and bleeding complications directly related to treatment-induced profound and prolonged pancytopenia, typically requiring multiple blood and platelet transfusions. Jehovah's Witnesses are often denied these procedures because of the fear of unacceptable mortality rates. In those patients unwilling to accept blood transfusions, various supportive techniques, including the glycoprotein hormone erythropoietin, may safely allow more aggressive treatment options [2].

We treated a 30-year-old Jehovah's Witness with recurrent non-Hodgkin's lymphoma (NHL) with high-dose chemotherapy, followed by autologous peripheral stem-cell transplant. This patient was first diagnosed with intermediate grade, B-cell non-Hodgkin's lymphoma. He received three months of VACOP-B chemotherapy with doxorubicin, cyclophosphamide, prednisone, bleomycin, vincristine, and etoposide, followed by 4,050 rads of radiation therapy. Seven months later, this patient returned with a large renal mass. Salvage chemotherapy with four cycles of decadron, ifosphamide, cisplatin, and etoposide induced a second remission.

After much discussion of the possible risks, this patient decided to undergo high-dose chemotherapy with peripheral stem-cell support. Cells were harvested by apheresis, with 5 mcg/kg of G-CSF growth factor administered twice daily for mobilization. He was then admitted to the hospital where he underwent an intensive chemotherapy regimen consisting of 6 g/m^2 cyclophosphamide, 2,100 mg/m^2 etoposide, and 300 mg/m^2 carmustine (BCNU) over 5 days. This individual was reinfused with 7.28×10^8 mononuclear cells/kg, consisting of 10.5×10^6 CD34$^+$ cells/kg and 90×10^4 colony-forming units/kg. In an attempt to avoid profound anemia, he was given 10,000 units of erythropoietin every day with 325 mg of ferrous sulfate three times a day, beginning 2 weeks prior to his high-dose chemotherapy. To limit iatrogenic blood loss, tests were performed every other day, drawing only 1–2 ml into pediatric vials. To prevent bleeding during the period of thrombocytopenia he was given 2 g of aminoceaproic acid every 6 hr.

In this patient, erythropoietin priming stimulated red blood cell production within the first 2 weeks of administration, as evidenced by an increase in his hemoglobin from 8.8 g/dl to 11.7 g/dl. The patient's blood counts were monitored as an outpatient during the engraftment period, with the lowest hemoglobin value of 9.7 g/dl seen on day 13 following reinfusion. For our prior 8 patients undergoing this procedure without erythropoietin priming, the hemoglobin fell an average of 5.4 g/dl below baseline, as compared to his 2 g/dl decrease, with 6 of the prior patients requiring transfusions. The present patient's absolute neutrophil count (ANC) rose above 1,000 on day 8 after reinfusion while platelets reached 20,000 on day 9, and 50,000 on day 13. After 50 days, he was able to resume an exercise program with a hemoglobin level at 12.9 g/dl. The patient experienced no major complications during the transplant directly related to anemia or thrombocytopenia.

Erythropoietin has the potential to reduce or limit blood transfusions, following high-dose chemotherapy. If hemoglobin levels can be elevated before and during the 2-week engraftment period, unnecessary or undesired blood transfusions can be avoided. The ability to predict if and how rapidly a patient will experience accelerated erythrocyte production from erythropoietin, so that the minimum time course and optimal dosage can be